AMENDMENTS TO THE SPECIFICATION:

Please replace the paragraph beginning at page 7, line 21 with the following amended paragraph:

Figures 4(A)-4(C) provide graphs of experiments indicating the levels of protection against *in vitro* proteolysis for IFNα-2b variants produced in mammalian cells. In Figures 4(B) and 4(C), the vertical axis indicates the relative level of ~~non-proteolized~~ non-proteolyzed protein and the horizontal axis indicates time in hours.

Please replace the paragraph beginning at page 8, line 21 with the following amended paragraph:

Figures 6(E) and 6(F) provide graphs indicating the levels of protection against *in vitro* proteolysis for IFNα-2b variants produced in bacteria. In Figures 6(E) and 6(F), the vertical axis indicates the relative level of ~~non-proteolized~~ non-proteolyzed protein and the horizontal axis indicates time in hours. The percent of residual (anti-viral) activity for the variants (gray circles with continuous lines) after treatment were compared to the treated wild-type IFNα-2b (solid circles with dashed lines).

Please replace the paragraph beginning at page 9, line 27 with the following amended paragraph:

Figure 6(O) provides graphs indicating the levels of protection against *in vitro* proteolysis for IFNβ variants produced in mammalian cells. Figure 6(N), the vertical axis indicates the relative level of ~~non-proteolized~~ non-proteolyzed protein and the horizontal axis indicates time in hours. The percent of residual (anti-viral) activity for the variants after treatment were compared to the treated wild-type IFNβ.

Please replace the paragraph beginning at page 10, line 26 with the following amended paragraph:

Figure 7(B) depicts a side view ribbon representation of IFNα-2b structure ~~(PDB code 1ITF)~~. Residue representation is as in FIG7A.

Please replace the paragraph beginning at page 11, line 1 with the following amended paragraph:

Figure 8(B) illustrates a structural overlapping between human interferon α-2b obtained from the NMR structure of IFNα-2a (PDB code 1ITF) and human interferon β (PDB code 1AU1) using Swiss [[Pdb]] PDB Viewer.

Please replace the paragraph beginning at page 11, line 4 with the following amended paragraph:

Figure 8(C) illustrates a structural overlapping between human interferon α-2b obtained from the NMR structure of IFNα-2a (PDB code 1ITF) and erythropoietin (PDB code 1BUY) using Swiss [[Pdb]] PDB Viewer.

Please replace the paragraph beginning at page 11, line 7 with the following amended paragraph:

Figure 8(D) illustrates a structural overlapping between human interferon α-2b obtained from the NMR structure of IFNα-2a (PDB code 1ITF) and granulocyte-colony stimulating factor (PDB code 1CD9) using Swiss [[Pdb]] PDB Viewer.

Please replace the paragraph beginning at page 54, line 24 with the following amended paragraph:

(2) Since protease mixtures in the body are quite complex in composition, almost all the residues in any target protein potentially are targeted for proteolysis ~~(FIG6A)~~ (FIG1A). Nevertheless, proteins form specific tri-dimensional structures where residues are more or less exposed to the environment and protease action. It can be assumed that those residues constituting the core of a protein are inaccessible to proteases, while those more "exposed" to the environment are better targets for proteases. The probability for every specific amino acid to be "exposed" and then to be accessible to proteases can be taken into account to reduce the number of is-HIT. Consequently, the methods herein consider the analysis with respect to solvent "exposure" or "accessibility" for each individual amino acid in the protein sequence. Solvent accessibility of residues can alternatively be estimated, regardless of any previous knowledge of specific protein structural data, by using an algorithm derived from empirical amino acid probabilities of accessibility, which is expressed in the following equation (Boger et al., Reports of the Sixth International Congress in Immunology, p. 250, 1986):

Please replace the paragraph beginning at page 133, line 18 with the following amended paragraph:

Antiviral activity of IFN α-2b was determined by the capacity of the cytokine to protect [[Hela]] HeLa cells against EMC (mouse encephalomyocarditis) virus-induced cytopathic effects. The day before, [[Hela]] HeLa cells (2×10^5 cells/ml) were seeded in flat-bottomed 96-well plates containing 100 µl/well of Dulbecco's MEM-GlutamaxI-sodium pyruvate medium supplemented with 5% SVF and 0.2% of gentamicin. Cells were growth at 37°C in an atmosphere of 5% CO_2 for 24 hours.

Please replace the paragraph beginning at page 133, line 25 with the following amended paragraph:

Two-fold serial dilutions of interferon samples were made with MEM complete media into 96-Deep-Well plates with final concentration ranging from 1600 to 0.6 pg/ml. The medium was aspirated from each well and 100 µl of interferon dilutions were added to [[Hela]] HeLa cells. Each interferon sample dilution was assessed in triplicate. The two last rows of the plates were filled with 100 µl of medium without interferon dilution samples in order to serve as controls for cells with and without virus.

Please replace the paragraph beginning at page 134, line 1 with the following amended paragraph:

After 24 hours of growth, a 1/1000 EMC virus dilution solution was placed in each well except for the cell control row. Plates were returned to the CO_2 incubator for 48 hours. Then, the medium was aspirated and the cells were stained for 1 hour with 100 µl of Blue staining ~~solutio~~ solution to determine the proportion of intact cells. Plates were washed in a distilled water bath. The cell bound dye was extracted using 100 µl of ethylene-glycol mono-ethyl-ether (Sigma). The absorbance of the dye was measured using an Elisa plate reader (Spectramax). The antiviral activity of IFN α-2b samples (expressed as number of IU/mg of proteins) was determined as the concentration needed for 50% protection of the cells against EMC virus-induced cytopathic effects. For proteolysis experiments, each point of for the kinetic measurements was assessed at 500 and 166 pg/ml in triplicate.

Please replace the paragraph beginning at page 135, line 1 with the following amended paragraph:

After 72 hours of growth, 20 µl of Cell titer 96 Aqueous one solution reagent (Promega) was added to each well and incubated 1H30 at 37°C in an atmosphere of 5% CO_2. To measure the amount of colored soluble formazan produced by cellular reduction of the MTS, the absorbance of the dye was measured using an Elisa plate reader ~~(spectramax)~~ (Spectramax) at 490nm.

Please replace the paragraph beginning at page 137, line 8 with the following amended paragraph:

Because IFNα-2b is administered as a therapeutic protein in the blood stream, a set of proteases was identified that were expected to broadly mimic the protease contents in serum. From that list of proteases, a list of the corresponding target amino acids was identified (shown in parenthesis) as follows: α-chymotrypsin (F, L, M, W, and Y), endoproteinase Arg-

C (R), endoproteinase Asp-N (D), endoproteinase Glu-C (E), endoproteinase Lys-C (K), and trypsin (K and R) Carboxypeptidase Y, which cleaves non-specifically from the carboxy-terminal ends of proteins, was also included in the protease mixture. The distribution of the target amino acids over the protein sequence spreads over the complete length of the protein, suggesting that the protein is potentially sensitive to protease digestion all over its sequence ~~(FIG6A)~~ (FIG1A). In order to restrict the number of is-HITs to a lower number of candidate positions, the 3-dimensional structure of the IFNα-2b molecule (PDB code 1RH2) was used to identify and select only those residues exposed on the surface, while discarding from the candidate list those which remain buried in the structure, and therefore stay less susceptible to proteolysis ~~(FIG6B)~~ (FIG1B).

Please replace the paragraph beginning at page 137, line 33 with the following amended paragraph:

To select the candidate replacing amino acids for each is-HIT position, PAM250 matrix based analysis was used ~~(FIG7)~~ (FIG2). In one embodiment, the two highest values in PAM250 matrix, corresponding to the highest occurrence of substitutions between residues ("conservative substitutions" or "accepted point mutations"), were chosen ~~(FIG8)~~ (FIG3). Whenever only a conservative substitution was available for a given high value of the PAM250, the following higher value was selected and the totality of conservative substitutions for this value was considered. The replacement of amino acids that are exposed on the surface by cysteine residues (as shown in ~~(FIG8)~~ (FIG3), while replacing Y by H or I) was explicitly avoided, since this change would potentially lead to the formation of intermolecular disulfide bonds.

Please replace the paragraph beginning at page 138, line 11 with the following amended paragraph:

Thus, based on the nature of the challenging proteases, and on evolutionary considerations as well as protein structural analysis, a strategy was defined for the rational design of human IFNα-2b mutants having increased resistance to proteolysis which could produce therapeutic proteins having a longer half-life. By using the algorithm PROTEOL (see, e.g., infobiogen.fr), a list of residues along the IFNα-2b sequence was established, which can be recognized as a substrate for different enzymes present in the serum. Because the number of residues in this particular list was high, the 3-dimensional structure of IFNα-2b obtained from the NMR structure of IFNα-2a (PDB code 1ITF) was used to select only those residues exposed to the solvent. Using this approach, 42 positions were identified, which

numbering is that of the mature protein (SEQ ID NO:1): L3, P4, R12, R13, M16, R22, [[K23]] R23, F27, L30, K31, R33, E41, K49, E58, K70, E78, K83, Y89, E96, E107, P109, L110, M111, E113, L117, R120, K121, R125, L128, K131, E132, K133, K134, Y135, P137, M148, R149, E159, L161, R162, K164, and E165. Each of these positions was replaced by amino acid residues, such that they are defined as compatible by the substitution matrix PAM250 while at the same time the replacement amino acids do not generate new sites for proteases.

Please replace the paragraph beginning at page 139, line 25 with the following amended paragraph:

A top and side view of IFNα-2b structure in ribbon representation (obtained from NMR structure of ~~IFNα-2b~~ IFNα-2a, PDB code 1ITF) depict residues in "space filling" defining (1) the "receptor binding region" as deduced either by "alanine scanning" data and studies by Piehler et al., *J. Biol. Chem.*, 275:40425-40433, 2000, and Roisman et al., *Proc. Natl. Acad. Sci USA*, 98:13231-13236, 2001, and (2) replacing residues (LEADs) for resistance to proteolysis.

Please replace the paragraph beginning at page 153, line 23 with the following amended paragraph:

Antiviral activity of IFN β was determined by the capacity of the cytokine to protect [[Hela]] HeLa cells against EMC (mouse encephalomyocarditis) virus-induced cytopathic effects. The day before, [[Hela]] HeLa cells (2 x 10^5 cells/ml) were seeded in flat-bottomed 96-well plates containing 100 µl/well of Dulbecco's MEM-GlutamaxI-sodium pyruvate medium supplemented with 5% SVF and 0.2% of gentamicin. Cells were growth at 37°C in an atmosphere of 5% CO_2 for ~~24 hours~~
~~Two-fold~~ 24 hours. Two fold serial dilutions of interferon samples were made with MEM complete media into 96-Deep-Well plates with final concentration ranging from 1600 to 0.6 pg/ml. The medium was aspirated from each well and 100 µl of interferon dilutions were added to [[Hela]] HeLa cells. Each interferon sample dilution was assessed in triplicate. The two last rows of the plates were filled with 100 µl of medium without interferon dilution samples in order to serve as controls for cells with and without virus.

Please replace the paragraph beginning at page 153, line 5 with the following amended paragraph:

After 72 hours of growth, 20 µl of Cell titer 96 Aqueous one solution reagent (Promega) was added to each well and incubated 1H30 at 37°C in an atmosphere of 5% CO_2.

To measure the amount of colored soluble formazan produced by cellular reduction of the MTS, the absorbance of the dye was measured using an Elisa plate reader ~~(spectramax)~~ (Spectramax) at 490nm.